REMARKS

Favorable reconsideration is respectfully requested in view of the foregoing amendments and following remarks.

Claims 2, 4 and 12-35 have been cancelled without prejudice.

Claim 1 has been amended to incorporate the limitations of claim 4 and to further define the diamine according to this description of the specification at page 13, lines 26-27. Other minor editorial changes have been made which are self-explanatory. The term "diamine" in claim 8 has similarly been amended as in claim 1.

The foregoing amendments are deemed to overcome the rejection of claims 2, 4 and 10-11 under 35 USC 112, first paragraph.

Claims 1-4 are rejected under 35 USC 102 as anticipated by U.S. Patent No. 4,910,225 to Ogawa et al. This ground of rejection is deemed to be overcome in view of the foregoing amendments.

Re: Characteristics of the Claimed Method

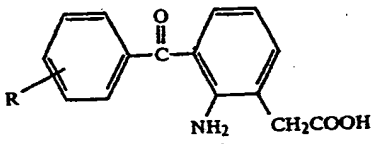
The claimed method for treating inflammatory eye disease is characterized by administering the combination of (1) an aqueous eye drop comprising (1) bromfenac and (ii) an organic amine selected from the group consisting of an amino acid, an alkanolamine, ethylenediamine, trimethylenediamine, a piperazine and an aminoalkylsulfonic acid, and (2) maintaining a therapeutically effective concentration of bromfenac in the anterior aqueous humor for at least 24 hours after the intraocular administration.

Based on the combination of limitations (a) bromfenac, (b) an organic amine selected from the group consisting of an amino acid, an alkanolamine, ethylenediamine, trimethylenediamine, a piperazine and an aminoalkylsulfonic acid, and (c) maintaining a therapeutically effective concentration of bromfenac in the anterior aqueous humor for at least 24 hours after the intraocular administration, the aqueous eye drop of the present invention exerts excellent effect of treating inflammatory diseases, such as blepharitis, conjunctivitis, scleritis, postoperative inflammation and uveitis.

As stated in detail below, a penetration test into the aqueous humor (Experimental Example 1 of the specification) and a medicinal efficacy test in a model rabbit of anterior chamber puncture (Experimental Example 2 of the specification) clearly demonstrate the excellent effect of maintaining a therapeutically effective concentration of bromfenac in the anterior aqueous humor for treating inflammatory diseases of the present invention.

Re: Rejection of claims 1-4 under 35 U.S.C. 102 over Ogawa et al.

Ogawa et al. describe an ophthalmic composition for inflammatory eye disease which comprises benzoylphenylacetic acid of the formula:

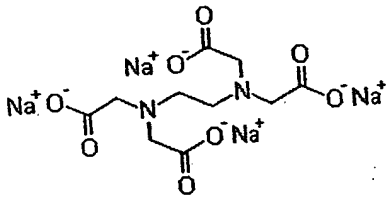


wherein R is hydrogen or halogen atom.

However, Ogawa et al. does not describe administering an aqueous eye drop comprising the combination of (1) bromfenac or its pharmacologically acceptable salt or a hydrate thereof and (ii) at least one organic amine selected from the group consisting of an amino acid, an alkanolamine, ethylenediamine, trimethylenediamine, a piperazine and an aminoalkylsulfonic acid.

Actually, Ogawa et al. describe on column 4, lines 33-34 sodium edetate as one example of the chelating agent which may be added to the ophthalmic composition.

However, sodium edetate is represented by the formula:



It is clear that sodium edetate is structurally different from the ethylenediamine and trimethylenediamine used in the claimed method.

Further, there is no disclosure in Ogawa et al. about "maintaining a therapeutically effective concentration of bromfenac in the anterior aqueous humor of the eye for at least 24 hours after the intraocular administration" of the present invention.

Thus, the claimed method as amended is novel and not anticipated by Ogawa et al.

Re: Rejection of claims 10-11 under 35 USC 103 over Ogawa et al. in view of U.S. Patent No. 5,945,121 to Kato et al.

Ogawa et al. neither mentions nor suggests administering an aqueous eye drop comprising the combination of (i) bromfenac and (ii) specific organic amines as defined in amended claim 1. Further, Ogawa et al. neither mentions nor suggests "maintaining a therapeutically effective concentration of bromfenac in the anterior aqueous humor for at least 24 hours after the intraocular administration" of the claimed method.

Kato et al. describe liposome eye drops comprising taurine (i.e., 2-aminoethanesulfonic acid), glucose and inorganic salts, which are useful for treating dry eye or mitigating its symptoms. Taurine is used as an active ingredient in Kato et al. On the other hand, bromfenac is an active ingredient in the present invention. Thus, the active ingredient of the claimed method and Kato et al. is different from each other.

Further, in Kato et al., bromfenac is not mentioned nor suggested anywhere. Kato et al. describes on column 2, lines 6 to 34 that "...it is possible to contain further components or other active ingredients, ...for example, neostigmine, methyl sulfate, anti-inflammatory agents (e.g. dipotassium glycyrrhizinate, e-aminocaproic acid, allantoin, berberine chloride, berberine sulfate, sodium azulene sulfonate, zinc sulfate, zinc lactate, lysozyme chloride, etc.) ... sulfa drugs and like". Thus, Kato et al. describe a large number of drugs which may be added. However, bromfenac is not mentioned nor suggested at all.

In the claimed method, intraocular penetration of bromfenac is promoted not only by addition of an organic amine such as taurine but also by addition such organic amines as trometamol which has nothing to do with anti-inflammatory activity. The unexpected effect of this invention of promoting the intraocular penetration of bromfenac is caused by interaction between bromfenac and the specific organic amines as defined in amended claim 1.

In addition, the object of Kato et al. is to provide eye drops which have mitigating and treating effects on symptoms caused by dry eye (please see column 1, lines 22-24). On the other hand, the object of the present invention is to provide aqueous eye drops which promote intraocular penetration and prolong retention time of bromfenac in the anterior aqueous humor of the eye for treating inflammatory diseases. Thus, the object of the instant invention is different from Kato et al.

For the foregoing reasons, the claimed method is unobvious over Kato et al. to a person skilled in the art.

Endo et al. describe that taurine is effective in suppressing the release of histamine. Huth, U.S. Patent Publication No.2004/0120916, describes a contact lens solution comprising taurine, an antimicrobial component which prevents losses in ocular tissue membrane integrity during contact lens wear.

However, maintaining a therapeutically effective concentration of bromfenac in the anterior aqueous humor, and treating inflammatory diseases of eye, are not mentioned nor suggested in Endo et al. and Huth.

The Unexpected Excellent Effect of the Claimed Method

An eye drop of the present invention shows excellent effect of maintaining a therapeutically effective concentration of bromfenac in the anterior aqueous humor for at least 24 hours after the intraocular administration, for treating inflammatory diseases of the eye.

Intraocular penetration of bromfenac is promoted not only by addition an organic amine such as taurine but also by addition of trometamol which has no relation with anti-inflammatory activity. This effect is caused by interaction between bromfenac and the specific organic amines as defined in amended claim 1.

The excellent effect of the present invention is apparent from Experimental Examples 1 and 2 on page 20, line 2 to page 26, line 2 in the specification as originally filed.

Experimental Example 1

A penetration test into the aqueous humor was conducted using formulation 1 (Bromfenac + Boric acid) , formulation 2 (Bromfenac + trometamol*) and formulation 3 (Bromfenac + aminoethylsulfonic acid)

*trometamol is 2-amino-2-(hydroxymethyl)propane-1,3-diol.

Results are shown on Table 3

Table 3

Test formulations (eye drops, pH 7.8)	*Bromfenac (ng/ml,)* in the aqueous humor 2 hours after the intraocular administration
formulation 1 (no addition of an organic amine)	214 ± 46
formulation 2 (addition of trometamol)	260 ± 45
formulation 3 (addition of aminoethylsufonic acid)	350 ± 123

Table 3 shows that the concentration of Bromfenac in the aqueous humor 2 hours after the intraocular administration increased about 1.2 times in case of the formulation 2 (addition of trometamol) and about 1.6 times in case of the formulation 3 (addition of aminoethylsufonic acid) compared to the eye drop of formulation 1 (no addition of an organic amine).

Experimental Example 2

A medicinal efficacy test in a model rabbit of anterior chamber puncture was conducted using formulation 4 (Bromfenac + Boric acid), formulation 5 (Bromfenac + 0.5g aminoethylsulfonic acid) and formulation 6 (Bromfenac + 1.0g aminoethylsulfonic acid)

An inhibition rate of inflammation after the puncture of anterior chamber was calculated according to the following equation.

Inhibition rate (%) = ((Average flare value in the anterior chamber of the control group) minus (Average flare value in the anterior chamber of the test material administered group))/ (Average flare value in the anterior chamber of the control group) x 100

Results are shown on Table 5

Table 5

Test formulations (eye drops)	Inhibition rate (%) (24 hours after administration)
Formulation 4 (pH 8.3) (no addition of an organic amine)	0.3 (n=6)
Formulation 5 (pH 7.8) (addition of 0.5g aminoethylsufonic acid)	25.5 (n=7)
Formulation 6 (pH 7.0) (addition of 1.0g aminoethylsufonic acid)	73.9 (n=10)

Table 5 shows the inhibition rate of inflammation after the puncture of anterior chamber, which was calculated by the measured flare value in the anterior chamber. The inhibition rate of the formulation in which no aminoethylsulfonic acid was added (Formulation 4) was 0.3% at 24 hours after the puncture.

On the other hand, the inhibition rate of formulation 5 was 25.5% and the inhibition rate of formulation 6 was 73.9%, both of the formulations containing with aminoethylsulfonic acid.

Such effect is excellent and unexpected over the cited prior art references to a person skilled in the art. Even if Ogawa et al. is combined with the teachings of the other cited references (Kato et al. and so forth), this effect of the present invention is not obvious at all.

In summary, even if the teachings of the references are combined, they do not teach or suggest the claimed method of administering the claimed combination for treating inflammatory eye disease, which has the unexpected effect of maintaining a therapeutically effective concentration of bromfenac in the anterior aqueous humor of the eye for at least 24 hours after the intraocular administration.

In view of the foregoing, it is believed that each ground of rejection set forth in the Official Action has been overcome, and that the application is now in condition for allowance. Accordingly, such allowance is solicited.

Respectfully submitted,

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